MEDICAL STAFF CONFERENCE

Changing Drug Patterns in the Haight-Ashbury

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SCHMID:* We have a special subject this morning: Changing drug patterns in the Haight-Ashbury. We have no patient today to present to you, but fortunately we have Dr. David E. Smith to discuss the subject. Dr. Smith is Medical Director of the Haight-Ashbury Medical Clinic, Assistant Clinical Professor at the University of California San Francisco Medical Center, Lecturer in Criminology at the University of California at Berkeley, and Editor of the *Journal of Psychedelic Drugs.*

DR. SMITH: For better or for worse, San Francisco was the "acid"† capital of the world for a long time, and now it has become the "speed"‡ capital of the world.

My presentation on "Changing Drug Patterns in the Haight-Ashbury" will be based on my clinical experience at the Haight-Ashbury Medical Clinic and at San Francisco General Hospital, and on research conducted through the Department of Pharmacology under the direction of Dr. Frederick Meyers entitled "Drug Practices in the Haight-Ashbury Subculture." In reference to the effects of chronic LSD use, I will be presenting some very good work done by Dr. Kay Blacker and his group at Langley Porter Neuropsychiatric Institute in which a group of chronic LSD users was studied in depth.

For those physicians who have had little experience or little understanding of youthful drug abuse, I want to begin by presenting a few basic facts. So many people, particularly in the medical community, focus only on the drug factors. It is quite apparent that in analyzing the drug reaction, drug factors or the agents of drug abuse represent only part of the overall reaction, while personality and group factors represent the other crucial variables.[2] We must realize that a drug interacts with a particular individual who is at the same time interacting with those around him in the immediate drug environment. In addition, group or cultural factors influence his mental set or attitude toward his drug experience. By altering any one of these variables it is possible to alter the acute drug reaction and influence the chronic drug pattern.

In the Haight-Ashbury district of San Francisco, methamphetamine abuse has become the major youthful drug problem. The "speed freak" has replaced or "driven away" the "acid head," and as a result Haight-Ashbury has been converted from an acid subculture to a speed subculture. I will begin this presentation with an appropriate clinical description.

*Rudi Schmid, M.D., Professor of Medicine.
†"Acid" is the street name for LSD.
‡"Speed" is the street name for methamphetamine.

High-Dose Methamphetamine Abuse: The Speed Cycle

To understand high-dose methamphetamine abuse, one must understand the manner in which it is taken. Like the user of any drug, the "speed freak" has certain motivations and expectations for his drug use. A parallel with alcohol use would familiarize this for the audience. You may have a martini during the week and set as your expectation relaxation. On Friday or Saturday, not having to get up the next morning, you set as your expectation intoxication and have three or four martinis, thus varying the dose to meet your goal. In all cases people have expectations from their drug use. It is important for the physician to attempt to understand these motivations for drug use not only as they bear on acute treatment but also with regard to chronic treatment and intervention of a potentially destructive life-style.

The person who uses high dose methamphetamine is seeking the "flash" or the "rush." In other words, he injects the substance and has a very rapid reaction which he describes as a "full body orgasm." The methamphetamine-induced excitation and agitation that follows is, in a "speed freak," a secondary consideration. He is after the initial phenomenon of the injection. The patient emphasizes that his objective from "shooting" speed is the flash or orgasmic feeling, and that the euphoria or sense of wellbeing is a secondary consideration. Individuals often start on oral methamphetamines and develop a desire for the "high," the excitation of the oral amphetamines. But for various reasons ranging from group pressure to personality problems they find that the intravenous injection of the substance is even more desirable, leading eventually to this distinctive and destructive pattern of drug use.

As you know, methamphetamine interrupts sleep patterns and suppresses appetite. The individual may go on a "speed binge" lasting three or four days in which he "shoots up" from one to ten times a day, always going for the peak experience. He does not eat or sleep during this time. He is in a continual state of hyperexcitement until, for one of various reasons, he decides to terminate this "speed binge." This may occur for several reasons—exhaustion and fatigue, abnormal psychological circumstances that are frightening to him, or inability to obtain the drug.

For whatever reason, the "speed binge" is terminated and we then see the reaction phase of the speed cycle. The reaction phase to the "speed binge" is classically the exhaustion syndrome. The individual often lapses into a deep sleep for periods of from 24 to 48 hours, depending on the duration of the "speed binge"; and upon awakening he may eat ravenously. The management of the exhaustion syndrome is relatively easy, and treatment consists primarily of supportive care. To contrast the speed cycle with the heroin cycle, when the heroin addict is intoxicated he may be sedated or "on the nod," whereas the intoxicated methamphetamine addict is hyperexcitable and agitated. After withdrawal from methamphetamine, a state of exhaustion exists, but in heroin withdrawal a state of excitation predominates. So we have a decided contrast between the intoxication and withdrawal phenomena of these two different drug dependencies.

I have described the action-reaction cycle, but unfortunately many of the amphetamine users do not return to a baseline level of personality function. They have a prolonged subacute phase in which profound depression dominates. Very often the "speed freak" shoots methamphetamine again to treat his depression and another cycle begins. The intensity of the post-speed depression cannot be overemphasized. As one 17-year-old girl said to me when I was attempting to motivate her for therapy, "Without speed I feel so lousy that I'd rather shoot speed and live for one week than live for 40 years without it." Very rapidly a situation of desperation develops in which the patient sees no hope for interruption of this pattern of drug use, and the only feasible therapy is to remove the individual from that drug-using subculture. There is a good institutional program at Mendocino State Hospital and there is a self-help out-patient program in the city of San Francisco directed by the Haight-Ashbury Clinic. But so long as the "speed freak" maintains himself in an area where many other persons are also using the drug, he has a great deal of difficulty resisting the temptation to "go back up" again.

Medical and Psychological Toxicity of High-Dose Methamphetamine Abuse

I would like now to discuss some of the psychological and physical complaints that develop as a result of high-dose methamphetamine use. Last summer we analyzed 310 cases of high-dose methamphetamine abuse seen at the Haight-Ashbury Clinic during a three-month period (June to September 1967).[3] This is an unusually large

number of intravenous drug users of this type, and it indicates that methamphetamine abuse has been present for some time. Approximately 40 percent of the patients came to the clinic with physical complaints, 60 percent with psychological complaints. This is important when one views a drug treatment facility as basically a psychiatric facility. The medical facility can very often serve as a contact point to encourage longer term therapy or to motivate the patient for treatment for his psychological problems.

As to the physical complaints, we saw an unusually high incidence of hepatitis, a bewildering array of urticarial reactions, abscesses, respiratory complaints, and acute abdominal complaints. In observing the patients, it became apparent that acute gastrointestinal distress or abdominal cramps are part of the high-dose methamphetamine syndrome. I will not go into detail about the physical complaints, however; I prefer to focus on the types of psychological consequences that develop. These consequences can be divided into five categories:

1. Anxiety reaction
2. Amphetamine psychosis
3. Exhaustion syndrome
4. Prolonged depression
5. Prolonged hallucinosis

The major psychological complaint encountered was the simple acute anxiety reaction. The individual had overdosed and had become acutely anxious, concerned, tremulous, often with tachycardia and somatic concerns. In talking about dosage I must emphasize that virtually all the methamphetamine now available is black market methamphetamine. It is not therapeutic diet pills diverted into an illegal market. It is mainly synthesized by black market laboratories, and therefore an accurate assessment of dosage is difficult to obtain. Although the average therapeutic dose for appetite suppression is 5 to 15 mg, because of the rapid tolerance that develops with this drug, the "speed freak" shoots between one and five grams a day. The tolerance varies so widely among various users, however, that one questions whether this is a physical or a psychological tolerance.[4,6]

The amphetamine psychosis is less common and is associated with three diagnostic characteristics: (1) Visual hallucinations, (2) auditory hallucinations, and (3) a well-defined system of paranoia including ideas of reference.[6] Paranoia is a characteristic part of the reaction and makes treatment difficult because the individual is very concerned about entering a hospital or encountering the police. He feels comfortable only in a street facility and very often even there questions concerning the police arise. As an example, I saw an 18-year-old white man who had been having an amphetamine psychosis. He had a very well-defined system of paranoia in which he felt that the police were after him and that his roommate and he had come to the Medical Clinic for help. Except for this system of paranoia and distracting hallucinations, he was remarkably lucid. During our interview a staff volunteer of the clinic, wearing a black leather jacket, crossed in front of the door. The patient jumped up and said, "I knew it! You're part of the plot!" and tried to run out the door. While restraining the boy, I called the volunteer and indicated that this was a member of the clinic staff who just happened to wear a black leather jacket. He calmed down immediately. The movement in and out of a paranoia delusional system can be very dramatic, and the physician may suddenly become part of that system. If the patient happens to be large or violent, the physician may be in some immediate jeopardy.

In the amphetamine psychosis certainly the major psychochemotherapy is anti-psychotic drugs of the phenothiazine type. For these psychotic reactions the physician must also give serious consideration to getting the patient into a hospital if facilities are available, since the psychotic symptoms often persist. For the anxiety reactions, long-acting sedatives are enough. However, the acute anxiety reaction is self-limiting, and many times the physician tends to overtreat. Transition from the action to reaction phase can be quite dramatic, and the consequences of the anxiety reaction can be easily handled with a supportive, nonthreatening environment and the cautious use of sedative medication.

I have talked about the exhaustion syndrome and the appearance of a tenacious reactive depression. I would also like to mention the phenomenon of prolonged hallucinosis in which the high-dose amphetamine user experiences persistent auditory and visual hallucinations for days and even weeks after the acute reaction has passed. Only a few of those who have an amphetamine psychosis manifest this prolonged reaction, and we are not certain if drug factors or personality factors play the major role in this drug-induced thought disorder.[2,4,5,6]

I want to close my discussion of chronic high-dose methamphetamine use by emphasizing the importance of group factors as a major contributor to amphetamine toxicity. In a series of animal experiments we found the LD50 of d-amphetamine to be 100 mg per kg when the drug was administered to white mice housed individually. When the animals were grouped together and the environmental conditions remained constant, the LD50 decreased to 25 mg per kg. In other words, simple aggregation of the animals increased the toxicity of the drug fourfold. In analyzing this phenomenon of aggregate amphetamine toxicity we found a polyphasic mortality curve. The mortality was high at the 25 mg per kg dose and then decreased, so that at 75 mg per kg the drug was less toxic than at 25 mg. It then increased again at 100 mg per kg where a second LD50 appeared. In analyzing this polyphasic mortality curve we found that at the 25 mg per kg dosage, the animals were in a hyperexcitable and agitated state in which the mechanism of death was actually that of one animal killing another. As the drug dose was increased the animals became preconvulsive. The dose was not high enough to cause convulsions (the mechanism of death at 100 mg per kg), but the animals were so disorganized that they could not mobilize directive attacks at one another.[5]

The Haight-Ashbury now has some resemblance to a giant mouse cage in that individuals are taking high-doses of central nervous system stimulants and interacting very often in a destructive fashion. It has become quite apparent that just taking the drug in the high density population situation increases the toxicity. It is very important for the physician to be aware of the phenomenon of aggregate toxicity. Treatment of any central nervous system stimulant reaction should put great emphasis on a quiet, supportive, nonthreatening environment. A caustic statement by the physician or a nurse bursting into the treatment room would constitute poor treatment in this situation. I hope that persons who are treating drug reactions will become aware of the importance of environmental group factors in treating both amphetamine and LSD reactions.

The "Acid Head"

I have discussed a situation in which a person who is chronically using methamphetamine becomes violent, hostile and hyperactive. The chronic LSD user, the "acid head," presents an entirely opposite picture. In our clinic population, individuals who were using methamphetamine chronically were approximately the same age as those who were using LSD chronically. There were significant differences, however, in personality types and socio-economic background between the two groups of drug users. Of greater significance, however, is the fact that the chronic LSD user developed a pattern of thought and behavior which was the antithesis of that described above in the chronic methamphetamine user. Rather than seeking a "flash" or a thrill as did the "speed freak," the chronic LSD user developed a complex set of motivations for his drug use involving self-spycho-analytic, pseudo-religious and creative aspirations.

To understand the chronic effects of LSD, however, one must understand the psycho-pharmacological effects of the drug. To begin with, the individual under the influence of LSD manifests very pronounced perceptual changes. Primarily these changes are illusionary phenomena (for example, objects changing shape and color). On the other hand, one may see the phenomenon of synesthesia in which one sensory phenomenon is translated into another (for example, a record player gives off colored vibrations or an individual smells purple). Teenagers are well aware of the phenomenon of synesthesia and have immortalized it in songs such as "Good Vibrations." The perceptual changes are the most pronounced of the phenomena that one finds, but hallucinatory activity—that is, the actual perception of an object in one's sensory environment without the physical manifestation of that object — is relatively rare with LSD. One also sees decided alterations in symbolic associations with sensory input. For example, an individual may see a red light and become enamored of the hue of the light rather than make the symbolic association that one stops at the red light. Pronounced alterations in ideational functioning also occur. Very often individuals who have taken LSD tend to feel that they have had a universal religious experience in which they have found the answer to life. They develop a rather elaborate philosophical position around this sensory pattern and very often, particularly in the young mind, carry this into their non-drug state. In other words, they do not say, "This is just a drug reaction that gave me this subjective or illusionary experience"; they say, "I've found the

answer to life!" If LSD is taken in a psychedelic information environment where other individuals have had the same experience, then the interpretation of psychedelic reality is reinforced. Repeated LSD experiences with friends supporting a positive interpretation of the LSD experience produces some very dramatic psychological changes in the "acid head." I have described this characteristic alteration in the chronic LSD user as the "psychedelic syndrome."[3]

The characteristics of this psychedelic syndrome are, first, a profound belief in non-violence. The "acid head's" rejection of physical aggression is so profound that very often one sees a change in diet to natural, vegetable foods; his rejection of killing is so great that he refuses to eat meat. Another of the significant characteristics of the individual who uses LSD chronically and develops the "psychedelic syndrome" is a belief in *magic*: Mental telepathy, astrology, extrasensory perception, mysticism, and telekinesia are all parts of his belief system. He believes that his mind can communicate and produce changes in his physical environment because his LSD experiences demonstrated this. The "acid head" develops a life-style based in this particular belief system. For example, an "acid head" may not come to work at the Haight-Ashbury Clinic because "the stars are wrong" or "it's impossible for me to interact or work with [some other person] because our signs conflict." Recently there developed a sincere belief that a meteorite was going to hit San Francisco and a large number in the community left town for Colorado.

Medical Significance of the "Psychedelic Syndrome"

What medical significance does the "psychedelic syndrome" have? Persons with "psychedelic syndrome" tend to group together in communal living situations, and it is a combination of chronic LSD usage and the psychedelic community that reinforces behavior of this type. They undergo a profound psychological conversion to belief in an unstructured psychedelic religion.

The medical significance of the "psychedelic syndrome" is vague. In Dr. Kay Blacker's studies[1] at the Langley Porter Institute no classical evidence of organic brain damage was found in chronic LSD users. On the other hand, he found with visually evoked electroencephalographic responses an increase in the number of low intensity visual responses. But in another test sensitive to intellectual disorganization or schizophrenia, the auditory two-toned evoked potential, the group of LSD users showed no abnormality. In other words, as Dr. Blacker pointed out, an alteration in one type of psychological testing which may be characteristic of a schizophrenic process does not imply an alteration in an entirely different type of psychological testing. His assumption is that the chronic LSD user tends to modulate and organize sensory input in a different and unique fashion. In other words, he views the world differently from the nonuser or the casual user of LSD. His subjects had intact and intense interpersonal relationships and could not, using standard nomenclature, be described as schizophrenic—merely as eccentric. The breakdown in interpersonal relationships occurs between the "hip" and the straight community or between the nonpsychedelic and the person who is involved in the psychedelic subculture. I believe there is mounting evidence that the young people who regularly use LSD and involve themselves in the psychedelic subculture develop a very profound alteration in psychosocial functioning.

What is the significance of this? Why do I belabor the point? I bring it up because many people seem to believe that young persons who are involving themselves with what can be called the psychedelic movement are going through a "phase" and will easily become "straight" again. The rationalization of those who hold this belief is that "these young people are just experimenting, as we did when we swallowed goldfish or went to fraternity games, and they will come back." It is my conjecture that at the very least the young people who are deeply and intensely involved in this movement will not easily be able to reenter the dominant American culture, because of a profound conflict in value systems. A person with the "psychedelic syndrome," committed to non-violence, will have great conflict in a society like ours where the ethic is violence and competition. I believe that the young people participating in the "hip" movement will not be able to reenter the dominant culture without having some very significant problems. So long as they remain in the psychedelic subculture their "psychedelic syndrome," with its characteristics of non-violence and magical beliefs, is actually respected. They cannot by the standards of that community be called mentally ill—only by the standards of our community. Therefore, so long as the individual remains in the psychedelic subculture, treatment of the "psychedelic syn-

drome" becomes as beneficial as treating some of our accepted religious institutions. Treatment is indicated and successful only if, for various reasons—monetary, parental, or whatever—the individual attempts to reenter the straight society. Reentry can cause severe psychological problems, and as a result "becoming straight" will be a much more difficult process than most adults predict.

On the other hand, the "acid head" community cannot live with the "speed freak" community because of the violent characteristics of the latter. As a result the "hippies" have left the Haight-Ashbury district, moving to the country where they can establish small rural communes which tolerate and reinforce their belief systems. Unfortunately, in the conflict of "speed freaks" against "acid heads," speed always drives out acid just as in the broader society the philosophy of violence always dominates the higher aspirations of non-violence, peace, and love.

DR. SCHMID: We have time for discussion and questions.

DR. WILLIAMS:* What proportion of people return to the straight society from the hippie society?

DR. SMITH: It must be emphasized that this movement is so recent that we do not have data to support an intelligent response to this question. In analyzing the population structure it is quite obvious that there exists a core or committed group and a large number of camp followers. ("Plastic hippies" is one term that has been used for the latter.) The majority of the younger people who move between the straight and hip society cannot themselves be called "hippies," in that they do not have an intense belief system. They are attracted to the music and certain of the statements that they have heard, but they are very unsuited to this life-style. This group, the teenage group, presents the major health and social problems in the community. It is impossible to state what proportions of such persons are converted and stay. With the introduction of speed as a dominant drug in the urban areas, it is progressively less and less. Unfortunately we are seeing a conversion not to a hippie life-style but a conversion to a compulsive drug-using life-style.

DR. EARLEY:† Are there any data available on the hard core, the inner core, so to speak, of the hippie community?

DR. SMITH: There is good evidence that the hippie subculture which contains hippies, sociopaths, militants, teenagers, plastic hippies, social scientists and newspaper reporters is still rapidly growing. I base this not so much on what we see in the Haight-Ashbury but on reports that I receive from across the country indicating that the total movement is increasing. I have received about fifteen consultation calls in the last six months about the hippie influx in other parts of the country. I have every reason to believe both from this information and from my personal observation in lecturing in other parts of the country that the hippie population is increasing.

Now, the direction of the movement is another problem. There is an initial phase of cooperation and sharing and philosophical idealism, and then the militants and thrill-seekers move in. That seems to be the natural history. To break up this pattern, the large communities in which these small subcultures develop must come to the conclusion that their own extremely negative reaction is the wrong approach. There is not a city yet that has said anything but, "You're not welcome. We won't give you anything." In other words, it appears that some city eventually will attempt to develop some specialized educational, medical, and social approaches in working with these alienated young people and, it is hoped, interrupt this negative trend.

QUESTION FROM AUDIENCE: What is the ethnic origin of the hippie culture?

DR. SMITH: We have every reason to believe that, at least in the initial stages, it is middle and upper-middle class Caucasian youths with the highest representation from the professional family background that mainly make up this group.

PHYSICIAN IN AUDIENCE: Would you comment on the therapeutic use of LSD in terminal cancer cases and in chronic alcoholics?

DR. SMITH: As you know, LSD has been suggested for these two disorders; and, as you also know, therapeutic research with LSD has virtually come to a halt in the United States. With regard to terminal cancer cases, there is virtually no work going on. There is a great deal of work on alcoholism going on in Canada, and we are receiving conflicting reports. Some of the initial reports were very optimistic, but a later report indicated that variables were not controlled. In other words, alcoholics who were given LSD were also given thera-

*Hibbard E. Williams, M.D., Associate Professor of Medicine.
†Laurence E. Earley, M.D., Associate Professor of Medicine.

peutics of other types—community environment and increased attention — that produced an increase in the cure rate. When these variables were controlled, there was little difference between groups that were treated with LSD and those that were not. The recent studies have focused more on repeated long-term use of LSD, and I think the best work on this is going on in Czechoslovakia.

DR. SOKOLOW:* What are the factors which determine whether a curious teenager will become a permanent hippie?

DR. SMITH: Many factors come to mind. I think we are seeing the first wave of the mass-educated pill-taking society. It is interesting that teenagers have found many of the new hallucinogens by consulting the toxicity comments about drugs in the medical literature. For example, we had a small wave of Symmetrel® abuse because its toxic manifestations include depersonalization and hallucinosis. I receive inquiries about different botanicals from teenagers, and they are incredibly curious about drugs. I do not answer letters about botanicals, but it is interesting that in reviewing patients' histories this statement occurs over and over: "My parents used these drugs, alcohol, tobacco, caffeine, sleeping pills, wake up pills, tranquilizers." They learn that drugs can produce psychological states.

The disturbing feature is the failure of young people to question drug use under any circumstances. They do not question whether they should use a drug or not use it, but rather what drug should they use. For example, in our research into the hip community, we learned that 45 percent of the people interviewed have taken unknown drugs. This is a very interesting indictment of our drug-taking society. Most of these individuals will take a drug without the slightest idea of what it does. We saw this in San Jose where 4,000 pills of unknown nature were passed out among 16,000 teenagers at a rock festival and most of the pills were consumed.

We have created a drug-taking society, and the young people have extended some of our basic attitudes into a situation that is now completely out of control. Once they have become enamored of the properties of various types of drugs and begin believing in the esoteric properties, these young people become very vulnerable to a culture that has as its basis the use of chemical agents to create various psychological states. If one accepts the assumption that a pill will relieve anxiety, then it is not difficult to expect a drug to induce a religious experience or to increase learning. I believe we are seeing a continuum in which neither the dominant culture nor the hip culture questions whether drugs should be used. It is always more a question of what drugs should be used to achieve a particular psychological state.

PHYSICIAN IN AUDIENCE: What relation does amphetamine use have to the alleviation of hostilities?

DR. SMITH: It is quite apparent that during adolescence all young people have hostilities. In going through the maturation process there are many complex problems, problems in sexuality and anger against parents. If individuals conclude that it is necessary to act out these hostilities and aggressions and that it is acceptable to take a drug in order to do so, then the whole country may act out in a violent manner. One of the reasons that marijuana is used is that it has sedative qualities and ability to relieve hostilities and antagonism. Young people become involved in the chronic use of LSD to handle their own internal aggressions and hostilities, but when they start using speed they externalize rather than internalize those aggressions. This is why I am concerned about speed. I am certainly not convinced that acting out an aggression does anything more than reinforce this attitude of hostility and aggression as a way to handling internal problems. People who take speed act out the natural hostilities and conflicts that one sees during the adolescent maturation process. It would be best if they could work them out without drugs. If they do select a drug (particularly speed) as a means for conflict-solving, the result may be destructive indeed.

DR. SCHMID: Thank you, Dr. Smith, for a presentation notable for both competence and compassion.

*Maurice Sokolow, M.D., Professor of Medicine.

GENERIC AND TRADE NAME OF DRUG

Amantadine HCL—*Symmetrel®*

REFERENCES

1. Blacker, K. H., Jones, R. T., Stone, G. C., and Pfefferbaum, D.: Chronic users of LSD: The acid heads, presented at the 1968 American Psychiatric Association, in press.
2. Meyers, F. M., and Smith, D. E.: Recommendations for California drug abuse research and treatment facilities, Calif. Med., 109:191, Sept. 1968.
3. Smith, D. E.: LSD and the psychedelic syndrome, Clinical Toxicology, in press.
4. Smith, D. E.: Physical vs. psychological dependence and tolerance in high-dose methamphetamine abuse, Clinical Toxicology, in press.
5. Smith, D. E., Fischer, C. M., Schonfeld, G., and Hine, C. H.: Behavioral mediators in the polyphasic mortality curve of aggregate amphetamine toxicity, J. Psychedelic Drugs, in press.
6. Smith, D. E., Fischer, C. M., and Smith, R.: Toxicity of high-dose methamphetamine abuse, J. Psychedelic Drugs, in press.